LETTERS TO THE EDITOR

Scope

Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation

Letters should be:

- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors

They may contain short tables or a small figure. **Please send a copy of your letter on disk.** Full instructions to authors appear in the January 1999 issue of *Heart* (page 104).

Randomised trials of new surgical procedures are necessary

SIR,—It was with some dismay that we read the editorials on the problems and pitfalls of randomised controlled trials (RCTs) for evaluating new procedures in general[1] and minimally invasive direct coronary artery bypass (MIDCAB) in particular.[2] Many of the opinions offered in the articles arise from problems encountered as a result of poor design, planning, and execution of RCTs rather than as a result of the methodology itself.

The timing of trials of new technologies is problematic. The ideal moment is between standardisation of the new technique and its wide dissemination, but this is often a very brief moment given the understandable enthusiasm for the newest methods. The "tidal wave" of new technology and the tendency to follow the "evaluation bypass" route in its introduction to the health service were two of the problems the National Health Service research and development strategy was set up to tackle. It is doing so by providing funding for scientific evaluation in RCTs, and minimally invasive cardiac surgery is one of the current priorities for research under the health technology assessment programme.

Many technologies have been widely adopted and then later shown to be ineffective or harmful—for example, prophylactic antiarrhythmic drugs in acute myocardial infarction. Nor can we assume that less invasive or apparently more convenient techniques will be more acceptable to patients. The much praised trial comparing laparoscopic and open surgery for cholecystectomy has shown no difference between the two in terms of hospital stay, patient discomfort, return to work, and complications.[3] Bonchek[1] suggests that meta-analysis of large clinical series can substitute for RCTs, but bias in observational studies may be considerable. Based on observational evidence that β carotene prevents lung cancer, an RCT was undertaken and showed that, on the contrary, the risk of lung cancer was significantly greater in the group assigned to receive β carotene.[4] If bias is not recognised, it may be magnified by incorporation into meta-analysis. In comparison, the potential bias from selection of suitable patients in RCTs is less misleading.

RCTs comparing surgical and medical management have particular problems; clinicians must see beyond the interests of their own specialty to ensure better overall patient management, based on good scientific evaluation of new practice. Objective criteria for patient selection are indeed important[1] and crossover of patients from the old to the new treatment should be discouraged. The US multicentre trial of PLC Systems' transmyocardial revascularisation laser treatment for patients with intractable angina was criticised by an FDA advisory committee for having too many "crossovers" from medical to surgical management and too brief follow up.[5] RCTs are costly and time consuming and should only be undertaken when definitive answers are to be gained to questions that are of importance to patients and the health service.

We believe that the time is right to conduct the first MIDCAB trial. Although the technique is still evolving, for most centres the main indication is an isolated proximal stenosis of the left anterior descending artery and a good comparison is with angioplasty, with or without stents, as clinically indicated in routine practice. Multidisciplinary collaboration is the lynchpin of the successful RCT; not just between different clinical specialties but with crucial research professionals such as medical statisticians and health economists. In addition, it is desirable that such trials are multicentred to provide rapid and generalisable results. Major research grant institutions and medical journals could play a role in encouraging multicentre and multidisciplinary collaboration to complete trials according to the best scientific practice, as quickly as possible. Editorials should encourage, rather than undermine, the use of scientific methodology to evaluate new procedures.[6]

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1 Bonchek LI. Randomised trials of new procedures: problems and pitfalls. *Heart* 1997;**78**:535–6.
2 Izzat MB, Yim APC, Sanderson JE. Minimally invasive direct coronary artery bypass: too young for a trial. *Heart* 1997;**78**:533–4.
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This letter was shown to Dr Bonchek who replies as follows:

I am disappointed that such distinguished scientists as Sharples *et al* reacted with "dismay" to my editorial. I thought that I had adequately emphasised the core of my message: most influential RCTs have compared drugs with drugs, or operations with operations. In contrast, most trials that have compared evolving operations with drug treatment have had unique problems that impaired their validity. (The reader is asked to review the references in my editorial and particularly reference 8 for historical examples that substantiate these assertions.)

These correspondents accuse me of undermining the use of RCTs for evaluating new procedures in general. I plead innocent to the charge, because my essential message was that well timed and properly designed RCTs that compare new procedures with established ones prevent the waste of scarce resources on ill designed comparisons between apples and oranges (that is, between drugs and surgery). My assertions about the difficulty of selecting the proper time for trials of evolving procedures are echoed by the correspondents' comment that the timing of trials of new technologies is problematic.

I am also accused of suggesting that meta-analysis of large clinical series can substitute for RCTs. In fact, the summary of my editorial defined the specific circumstances in which I felt that RCTs are likely to help and those in which they are not, after which I said that "meta-analysis of large clinical series can substitute for those randomised studies that are unlikely to be helpful."

Actually, Sharples *et al* inadvertently substantiate my assertions. Their examples of useful RCTs were invariably comparisons between different drug regimens (antiarrhythmics in myocardial infarction and β carotene to prevent lung cancer), or between different operations (laparoscopic *v* open surgery for cholecystectomy). The RCT they propose, minimally invasive coronary bypass (MIDCAB) versus angioplasty of the left anterior descending coronary, is a comparison between procedures, a circumstance in which I agree that RCTs can be informative if they adhere to certain design criteria that I was careful to specify. I made no reference to MIDCAB in my editorial, and was unaware of the editorial by Izzat *et al* until it was published, but their point of view seems unexceptional to me, as it merely advises proceeding deliberately. They acknowledge that RCTs of MIDCAB "will certainly be necessary at some stage." Surely, there is room for men of good will to disagree about the exact timing of such studies.

This letter was shown to Dr Izzat et al, who reply as follows:

We thank Dr Sharples and colleagues for their interest in our editorial. However, they seem to have misunderstood the purpose of our commentary. We are not against the concept of RCTs but if these are to be useful to clinicians rather than to statisticians then they have to be generally applicable. The differences between a drug trial and those involving a procedure were clearly highlighted and discussed by Bonchek. It is obvious that the technicalities of the MIDCAB procedure are evolving rapidly and if a trial is done in the very early stages before the many technical problems have been overcome then the procedure is likely to fair badly and be

condemned. This is not the way to make progress. Surgeons and interventional cardiologists need time to develop procedures and to overcome the learning curve before submitting their technique to an RCT especially if the comparison is with drug treatment. An RCT will have to be done with the MIDCAB procedure at some time but the most important question is when.

Although Sharples *et al* feel that the time is right to conduct the first MIDCAB trial, the only reason for this appears to be that the indications for MIDCAB are agreed on. However, they admit that the technique is still evolving. We all agree on the indications for MIDCAB, that is not difficult, but deciding when the technique has developed sufficiently to be subjected to a trial is another, more difficult question. We agree with their other comments about multidisciplinary and multicentre trials but they do not provide an answer to the difficult question: when is a technique ready to be subjected to an RCT? It cannot be in the early stages of development.

Cell adhesion molecules in cardiovascular disease: what can soluble levels tell us?

SIR,—Considerable research energy is being directed towards cell adhesion molecules, and the recent review by Hillis and Flapan[1] provides a useful introduction. As they allude to, blockade of the interaction between leucocytes and the endothelium by agents that mimic or inhibit these adhesion molecules may become a new class of therapeutic agent.[2 3] However, Hillis and Flapan only briefly draw our attention to the presence of soluble forms of these adhesion molecules in plasma.

The importance of these soluble forms is probably underestimated, as they may interfere with, or frustrate, attempts to reduce leucocyte–endothelial interactions in vivo, as has already been shown in vitro.[4 5] In addition, soluble adhesion molecules may be useful in dissecting the various pathophysiological events in cardiovascular disease, as it may be presumed that changes in concentrations may relate to activation or damage to various cells, such as the platelet and endothelium, which are pertinent to cardiovascular pathophysiology.

For example, the selectin family of adhesion molecules has three members, and corresponding soluble concentrations are measurable in the plasma. Soluble P selectin is believed to be the product of activated platelets, despite the endothelium having a membrane bound form.[6 7] Increased concentrations have been found in a number of conditions: thrombotic disorders, diabetes, and ischaemic heart disease. Importantly, raised concentrations in the last group of patients is predictive of adverse events.[8–10] Although increased concentrations of soluble E selectin are the result of cytokine activation of endothelial cells in vitro,[11] raised plasma concentrations have been reported in variant angina,[12] and in ischaemic heart disease[13]; in the latter group of patients, raised concentrations do not appear to predict adverse events.[14] Finally, it is still unclear whether concentrations of soluble L selectin, derived from leucocytes, are altered in ischaemic heart disease, although we have been unable to demonstrate significant differences between patients with peripheral atherosclerosis and healthy controls.[15] However, Siminiak and colleagues[16] recently reported raised concentrations within one hour to three days following admission for acute myocardial infarction.

The second major group of adhesion molecules belong to the immunoglobulin supergene family, and three members, with measurable soluble forms, warrant attention. Soluble intercellular adhesion molecule 1 (sICAM-1) is a likely product of many cells, including the endothelium and leucocytes. Also influenced by inflammatory cytokines in vitro,[11] raised sICAM-1 concentrations are found in many conditions, including angina[12] and both coronary artery disease and peripheral artery disease.[17] Raised concentrations in healthy men predict adverse events,[18] however, the association appears to be weak when there is already a background of existing atherosclerosis.[19] Conversely, vascular cell adhesion molecule 1 (sVCAM-1) does not seem to be increased in the plasma of patients with angina or coronary artery disease[12 17]: nor do concentrations predict adverse outcome.[19] However, concentrations do rise slowly (reaching a peak on day 3) after an acute myocardial infarction, and are moderately raised in some forms of peripheral atherosclerosis,[19] with some correlation with the extent of disease.[20 21] Soluble platelet endothelial cell adhesion molecule 1 (sPECAM-1) may also arise from many cells, including endothelial cells, platelets, and leucocytes. We have however been unable to find differences in the plasma of patients with coronary artery disease or peripheral artery disease compared to controls.[22]

Despite the above, a firm consensus about the significance and value of concentrations of soluble adhesion molecules in cardiovascular disease has yet to emerge, mainly due to some contradictory results. For example, Frijns *et al* have reported raised concentrations of soluble E selectin in ischaemic stroke and carotid atherosclerosis, whereas we have been unable to find increased concentrations in patients with peripheral atherosclerosis; conversely, unlike us, they failed to find raised sICAM-1.[17 23] De Caterina and colleagues[21] reported raised sVCAM-1 in peripheral atherosclerosis, whereas our group and Frijns *et al* have been unable to do so.[17 23]

It would be easy to jump to the conclusion that these inconsistencies are due to differences such as those of the type and degree of disease of the subjects, and/or laboratory methods, although most of the latter are commonly used commercial reagents. However, by and large, none of these essentially cross sectional studies have recruited particularly large (> 100) numbers of subjects, so that this may be one source of the inequalities. Until several large, hopefully prospective, studies are published, it seems likely that the simple immunohistochemical demonstration of cell adhesion molecules or the measurement of soluble adhesion molecules has little to offer current practising cardiologists in their quest for improved patient care. Nevertheless, the recognition that cell adhesion molecules do at least play some important role(s) in cardiovascular pathology is a small step forward in the complex field of vascular biology and pathophysiology.

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This letter was shown to Drs Hillis and Flapan, who reply as follows:

Drs Blann and Lip provide an excellent appraisal of the current state of research into the role of soluble adhesion molecules in cardiovascular disease. Although this is an area that was only mentioned briefly in our overview we agree that it is of interest and importance.

As they note, soluble adhesion molecules may affect the activity of leucocytes in vivo. Certainly, this has been demonstrated in vitro, where soluble E selectin is capable of increasing neutrophil β2 integrin expression and motility.[1] This may facilitate their adhesion to damaged arterial endothelium or, potentially, encourage their sequestration in capillary beds that would, in turn, reduce the numbers available at other sites.[2] An alternative possibility is that soluble adhesion molecules might reduce leucocyte adhesion and/or diapedesis by competing for binding sites or by less direct mechanisms.[3] Until such issues are resolved, and the precise contribution of each molecule is better understood, therapeutic use of systemic adhesion receptor analogues is some way off—local administration may be a more realistic approach in any case. Similarly, it may become possible within the next few years to combine improved vascular imaging with adhesion receptor labelled vehicles that are capable of binding to, and thus identifying, diseased and activated endothelium.[4]

While soluble adhesion molecules may complicate efforts to manipulate leucocyte–endothelial cell interactions serum concentrations could provide a useful insight as to the health of vascular endothelium. Raised plasma concentrations of sICAM-1 and, to a lesser extent, E selectin appear to be clearly associated with atherosclerosis,[5] while results regarding sVCAM-1 are less consistent.[5–7] Ridker *et al* have recently reported that sICAM-1 concentrations are independent predictors of future acute myocardial infarction[8] and, although it has been suggested that this association is weakened in patients with existing atherosclerosis,[6 9] the small numbers and diverse end points in the latter cohort make it difficult to draw any firm conclusions.

In addition to the increase of sICAM-1 in stable coronary artery disease, concentrations rise further in unstable disease[10 11]—presumably reflecting endothelial damage and activation. These early data exhibit a striking similarity to previous reports linking raised C reactive protein (CRP) to atherosclerosis and cardiovascular risk.[12 13] This suggests that sICAM-1 may serve as a more specific indicator of endothelial dysfunction and inflammation. However, while raised CRP is associated with adverse outcome in acute coronary syndrome, there have been no large trials assessing the predictive value of sICAM in this setting.

Whether soluble cell adhesion molecules prove to be useful diagnostic or prognostic indicators remains to be seen. There is increasing evidence that atherosclerosis shares many of the characteristics of a chronic inflammatory process, that infectious agents may be involved in its cause, and that infiltrating white cells contribute to the instability of atherosclerotic plaques.[14–16] It seems likely, therefore, that molecules that are so fundamental to the interactions between leucocytes and endothelium can give valuable insights into the mechanisms of coronary artery disease and possible outcome.

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Concentrations of angiotensin II, endothelin-1, and BNP in the coronary sinus and ascending aorta of patients with heart disease

SIR,—It has been well documented that neurohormonal mediators, such as the renin–angiotensin system,[1] endothelin,[2] and brain natriuretic peptide (BNP),[3] are severely activated in patients with congestive heart failure, and that the circulating concentrations of these mediators are good predictors of the severity of congestive heart failure and the prognosis. It has also been demonstrated that both angiotensin II and endothelin-1, like BNP, are locally expressed in cardiac tissue.[4–6] It is not clear, however, whether the increase in plasma concentrations of angiotensin II and endothelin-1 is caused by increased expression and spillover from cardiac tissue in patients with heart disease. To address this question, we measured the plasma concentrations of angiotensin II, endothelin-1, and BNP in blood withdrawn from both coronary sinus and ascending aorta in five patients subject to cardiac catheterisation.

All patients were studied in the morning and in a fasting state. Informed consent was obtained from each patient before the study. Coronary sinus blood was sampled using a 6 or 7 F catheter inserted via the right femoral vein. The position of the tip of the catheter was confirmed fluoroscopically and by blood oxygen saturation (mean (SD) 41 (3)%). Arterial blood was withdrawn using a 6 F pigtail catheter positioned in the ascending aorta adjacent to the coronary ostia, which was inserted via the femoral artery. Care was taken to use the same amount of time for drawing arterial blood samples as for the coronary sinus blood sampling. The blood samples were transferred to test tubes containing EDTA that were precooled with ice, and centrifuged immediately after at 1000 *g* for 10 minutes at 4°C. The plasma was stored at −20°C until analysis. The plasma concentrations of angiotensin II, endothelin-1, and BNP were determined by radioimmunoassay.

Table 1 shows the clinical characteristics, haemodynamic and echocardiographic data, and plasma concentrations of angiotensin II, endothelin-1, and BNP in both coronary sinus and ascending aorta. Patient 1, who had the most severe congestive heart failure among the five patients studied, had the highest plasma concentrations of angiotensin II, endothelin-1, and BNP in both the coronary sinus and ascending aorta. The plasma concentrations of angiotensin II and endothelin-1 in the coronary sinus were lower than or equal to those in the ascending aorta in all patients. In contrast, the plasma concentration of BNP was apparently higher in the coronary sinus than in the ascending aorta in all patients. The differences in BNP concentrations between the coronary sinus and ascending aorta were more prominent in

Table 1 Patient characteristics and plasma concentrations of neurohormonal mediators in coronary sinus (CS) and ascending aorta (AA)

Patient	Age/sex	NYHA class	Diagnosis	Mean PAP (mm Hg)	PCWP (mm Hg)	LVEDD (mm)	EF (%)	Angiotensin II (pg/ml)			Endothelin-1 (pg/ml)			BNP (pg/ml)		
								CS	AA	CS−AA	CS	AA	CS−AA	CS	AA	CS−AA
1	52/F	III	Cardiac sarcoidosis	35	27	59	32	11	12	−1	6.31	6.78	−0.47	982	563	419
2	69/M	III	ASD, Eisenmenger	62	2	32	76	5	6	−1	2.58	3.57	−0.99	418	374	44
3	68/M	II	Postanterior MI	13	4	47	71	0	5	−5	2.73	2.73	0.00	340	76	264
4	72/M	I	Angina pectoris	13	8	46	77	6	7	−1	2.07	2.10	−0.03	12	4	8
5	75/F	II	Postinferior MI	18	5	38	72	3	3	0	2.52	2.71	−0.19	82	41	41

NYHA class, New York Heart Association class; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; LVEDD, left ventricular end diastolic dimension; EF, ejection fraction determined by echocardiography; ASD, atrial septal defect; MI, myocardial infarction.

patients with higher BNP concentrations in the ascending aorta with the exception of patient 2, who had remarkable pulmonary hypertension.

These results suggest that, even though all three neurohormonal mediators appear to be good predictors of the severity of heart failure, the circulating concentrations of angiotensin II and endothelin-1 do not predominantly derive from cardiac tissue (unlike BNP, which predominantly derives from myocardium). Further investigation with a larger number of patients is needed to confirm this conclusion.

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Stamps in cardiology: foxglove

SIR,—The beautifully illustrated "Stamps in cardiology" on digitalis[1] was fascinating. Ever since my medical school days, I have been wondering about the reason behind the plant's common name—the foxglove. While it was easy to understand the Latin digitus in allusion to the finger-like blossoms of the plant; none of the professors around the world where I travelled to lecture could give me an explanation for foxglove.

Not long ago I read from *Medical meanings* by Haubrich[2] that "digitalis was proposed as the Latinised name for the plant in the 16th century by a German botanist, Leonard Fuchs (1501–66). Fuchs is German for 'fox'. Apparently, he chose digitalis, a Latin way of saying 'pertaining to the finger', because the common German name for the plant is Fingerhut, which means, literally, 'a finger hat' or thimble'."

I much prefer the explanation offered by Davies and Hollman—the fairies gave the flowers to foxes to wear on their feet so they could move in magic silence towards hens or away from men.[1] Perhaps some of your learned readers might know of other explanations.

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1 Davies MK, Hollman A. Digitalis and strophanthus: cardiac glycosides. *Heart* 1998;**80**:4.
2 Haubrich WS. *Medical meanings. A glossary of word origins*. Philadelphia: American College of Physicians, 1997:62.

Anomalous origin of the left coronary artery from the pulmonary artery

SIR,—Case 2 from this report[1] has subsequently been admitted with chest pain and polymorphic ventricular tachycardia (VT). This was initially treated with oral β blockers, but at electrophysiological testing the VT was still inducible. Coronary angiography showed no significant change from her previous angiogram. A myocardial perfusion scan with adenosine stress confirmed an anterior myocardial infarction with some flow reduction in the peri-infarct zone. There is difficulty in demonstrating reversible ischaemia in the presence of ALCAPA; however, she has been referred for surgical revascularisation and will be given an implantable cardioverter defibrillator if the VT remains inducible postoperatively.

A conservative strategy might be employed in this condition, however surgical intervention may still need to be considered for late complications.

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1 Nightingale AK, Burrell CJ, Marshall AJ. Anomalous origin of the left coronary from the pulmonary artery: natural history and normal pregnancies. *Heart* 1998;**80**:629–31.

NOTICES

The fourth European forum on quality improvement in health care and the **fourth Swedish QUL conference** will be held in Stockholm, Sweden, 25–27 May 1999. For further information, contact Ms Marchella Mitchell, BMA Conference Unit, BMA House, Tavistock Square, London WC1H 9JP, UK; tel: +44 (0)171 383 6478; fax: +44 (0)171 383 6869; email: mmitchell@bma.org.uk.

The third international meeting on interventional cardiology: frontiers in interventional cardiology will be held at the ICC Jerusalem International Conventional Center, Jerusalem, Israel, 27 June to 1 July 1999. There will also be a satellite symposium **Stenting and adjunctive pharmaceutical therapy**, 1–4 July in Eliat, Israel. For further information please contact Secretariat, 3rd International Meeting on Interventional Cardiology: Frontiers in Interventional Cardiology, PO Box 50006, Tel Aviv 61500, Israel; tel: +972 3 5140000; fax: +972 3 5175674/5140077; email: intercard@kenes.com.

The fourth world stroke congress will be held 25–29 November 2000 in Melbourne, Australia. For further information please contact ICMS Pty Ltd, 84 Queensbridge Street, Southbank, Victoria 3006, Australia; tel: +61 3 9682 024; fax: + 61 3 9682 0288; email: stroke@icms.com.au.